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Review

# Benefits of Controlled Ultraviolet Radiation in the Treatment of Dermatological Diseases

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## ABSTRACT

*Phototherapy is a second-line treatment modality for the most common dermatoses that is safe and effective. Most phototherapy regimens denote the use of ultraviolet (UV) radiation of different wavelengths in the management of several dermatoses. Currently, irradiations with broadband UVB (290–320 nm), narrowband UVB (311–313 nm), 308 nm excimer laser, UVA 1 (340–400 nm), UVA with psoralen (PUVA), and extracorporeal photochemotherapy (photopheresis) are being used. Beneficial effects of UV radiation are far from being completely understood. Dermatoses that may benefit from such approach are numerous, with psoriasis, parapsoriasis, atopic dermatitis, cutaneous T-cell lymphomas, morphea, and vitiligo vulgaris as main indications. UVB radiation primarily acts on cells at the epidermis and the epidermodermal junction, while UVA radiation affects epidermal and dermal components, especially blood vessels. UV radiation has immediate and delayed effects. Immediate effects are the formation of DNA photoproducts and DNA damage leading to apoptosis of keratinocytes, Langerhans cells, activated T-lymphocytes, neutrophils, macrophages, NK cells, fibroblasts, endothelial cells, and mast-cells, cell membrane damage by lipid peroxidation, and isomerization of chromophores such as urocanic acid. Delayed effects include synthesis of prostaglandins and cytokines that play important roles in immune suppression. Systemic and local immune suppression, alteration in cytokine expression (induction of interleukin-1 (IL-1) receptor antagonist, decrease in IL-2, increase in IL-10, IL-15), and cell cycle arrest may all contribute to the suppression of disease activity. PUVA is a form of controlled and repeated induction of phototoxic reactions which uses UVA light to activate chemicals known as psoralens. The conjunction of psoralens with epidermal DNA inhibits DNA synthesis and causes cell apoptosis. PUVA also causes an alteration in the expression of cytokines and cytokine receptors. Psoralens interact with RNA, proteins and other cellular components and indirectly modify proteins and lipids via singlet oxygen-mediated reactions or by generating of free radicals. Psoralens and UV radiation also stimulate melanogenesis with variable effects in patients with vitiligo vulgaris. Extracorporeal photopheresis is treatment modality used in management of erythrodermic cutaneous T-cell lymphomas. It is very potent in induction of lymphocyte apoptosis. Despite the introduction of numerous potent bioengineered systemic medications in the field of dermatology, phototherapy remains established, and often preferred, option for the most common dermatoses.*

***Key words:*** *apoptosis, nonionizing light, photobiology, photochemotherapy, phototherapy, ultraviolet therapy, tumor suppressor protein p53, NF-kappa B*

## Introduction

Phototherapy presents a physical form of treatment which uses an artificial ultraviolet (UV) radiation of different wavelenghts emitted from fluorescent lamps (with or without adding the photosensitiser) in the management of several dermatoses. UV radiation makes only 10% of the entire electromagnetic spectrum (200–400 nm). It is the biologically most potent part of the sunlight spectrum. UV light affects almost all epidermal and dermal cells: keratinocytes, Langerhans cells, endothelium, melanocytes, neutrophils, mastocytes, T-lymphocytes, fibroblasts and macrophages.

Disorders that may benefit from such approach are numerous, with psoriasis, atopic dermatitis, cutaneous T-cell lymphomas, morphea, and vitiligo as main indications.

Currently, phototherapy with broadband UVB (290–320 nm), narrowband UVB (311–313 nm), 308 nm excimer laser, UVA 1 (340–400 nm), UVA plus psoralen (PUVA),

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and extracorporeal photochemotherapy (photopheresis) are being used[1].

The interplay of the various photobiologic pathways is far from being completely understood.

## Ultraviolet B Therapy

According to the European protocol, UVB is the simplest form of phototherapy, as it refers to the use of artificial UVB radiation without additional exogenous photosensitizers. UVB radiation primarily penetrates into structures of the epidermis and superficial dermis[2].

The radiation is absorbed by the major endogenous chromophores with immunological importance, such as nuclear DNA, trans-urocanic acid, and cell membranes[1].

After UVB light absorption by nucleotides, covalent bonds start to form between two pyrimidine bases (thymine-thymine, cytosine-thymine, cytosine-cytosine rarest) and cyclobutane ring is created which causes growth arrest in keratinocytes, reversing epidermal acanthosis. This is the basic mechanism when treating psoriasis, parapsoriasis, pityriasis lichenoides chronica which have a significantly accelerated keratinocyte proliferation.

After single exposure, UVB light already upregulates expression of tumor suppressor gene p53. Affected under p53, individual keratinocytes will stop the cell cycle in G1 phase in order to facilitate DNA repair (pyrimidine dimer excision) before the cell enters into S phase of cell cycle (DNA replication occurs during this phase). Unless pyrimidine dimers are excised, individual keratinocytes undergo apoptosis (»sunburn cells«). It remains unknown why certain keratinocytes are more sensitive to UV radiation than others (senescent keratinocytes are more resistant to apoptosis than young keratinocytes)[3]. The upregulation of this tumor suppressor gene may be responsible for inhibition of keratinocyte turnover in psoriatic plaques[4].

UVB light causes photoisomerization of urocanic acid (UCA), another important chromophore within the *stratum corneum* of the epidermis. Upon UVB exposure, UCA is converted from trans-UCA to cis-UCA[5]. The presence of cis-UCA has local and systemic immunosuppressive effects via cutaneous cytokine modulation[6]. cis-UCA downregulates interleukin (IL)-12 (one of the crucial Th1 cytokines) production and enhances CD4+ T-cell IL-10 production, which could account for some of the immunosuppressive effects of UV radiation. Exposure of Langerhans cells to cis-UCA inhibits their ability to present antigen and induces immunosuppression.

Direct damage of DNA and accumulation of cis-UCA induce formation of reactive oxygen species and free radicals that can affect extranuclear molecular targets located in the cytoplasm and cell membane. These targets include cell surface receptors for epidermal growth factor (EGF), IL-1, and tumor necrosis factor (TNF), kinases, phosphatases, and transcription factors such as activator protein-1 (AP-1) and nuclear factor-kappa B (NF-$\varkappa$B). Devary et al. have found that UV response does not require a nuclear signal and is likely to be initiated at the plasma membrane. Lipid peroxidation of cell membrane may lead to activation of Src tyrosine kinases, which subsequently activate a cascade involving Ha-Ras, Raf-1, and JNK leading to the phosphorylation of c-jun and activation of the transcription factors AP-1 and NF-$\varkappa$B. Activation of NF-$\varkappa$B at the cell membrane following UVB exposure leads to T- lymphocytes apoptosis, which requires de novo protein synthesis, and increased membrane permeability which may also play a role in immunosuppression[7].

In addition to its effect on the cell cycle, UV light induces the release of prostaglandins and cytokines. Following UVB exposure, keratinocytes and lymphocytes secrete a number of pro-inflammatory cytokines such as IL-1, IL-10, and TNF-$\alpha$, which suppress Langerhans cells and thereby induce immunosuppression[8]. Several cytokines with important role in immune suppression, such as IL-6, IL-8, IL-10, IL-15, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prostaglandins, are released from UV-irradiated keratinocytes. Prostaglandin $E_2$ ($PGE_2$) is a potent mediator that inhibits the expression of co-stimulatory molecules on the surface of antigen-presenting cells and thereby prevents the activation of T-lymphocytes.

Keratinocytes and lymphocytes also upregulate Fas/FasL expression following UVB exposure and caspases are activated, resulting in nuclear DNA fragmentation and degradation of cellular structural proteins – laminin and actin.

Langerhans cells, the most important epidermal antigen-presenting cells, are highly susceptible to UVB irradiation, which reduces their number and alters their antigen-presenting function. Langerhans cells with altered antigen-presentig capacity leave the skin lesions and result in diminished response in the lymph node, which down-regulates systemic immune activation. The remaining dendritic cells acquire cytoskeleton damage by oxidative stress, and this reduces their ability to express high numbers of costimulatory surface markers to efficiently stimulate T cells. This mechanism has been proven to be effective in treatment of atopic dermatitis and cell-mediated (type IV) contact dermatitis. UVB exerts its action through direct phototoxic effect on T-lymphocytes in the dermoepidermal junction in patients with atopic dermatitis[1]. Interestingly, UVB is also effective in suppression of Staphylococcus aureus colonization in atopic dermatitis[9]. UVB can selectively reduce proinflammatory cytokine production in individual T cells, inhibiting Th-1 axis by IL-12, interferon-$\gamma$ (IFN-$\gamma$) and IL-8, which has a beneficial effect in psoriasis characterized by intraepidermal and perivascular T-cell infiltrates in the papillary dermis[10]. Another effect of phototherapy is its ability to reverse pathologic vessel architecture in psoriasis plaques and bring the elongated and tortuous capillary loops back to normal state.

UVB is effective in apoptosis of neutrophils, the major pathologic cells in Munro's microabscess of pustular psoriasis. Decreased expression of the adhesion molecules on

keratinocytes, macrophages and Langerhans cells is the basis of phototherapy of inflammatory dermatoses[11].

Broadband UVB involves 280–315 nm radiation, whereas lower wavelenghts can cause burns. In the past two decades, use of different fluorescent tube coatings has allowed development of narrowband UVB with a narrow emission peak at 311 nm wavelength.

According to obtained results from several controlled studies, narrowband UVB phototherapy is more efficient than conventional broadband UVB therapy, especially in the management of psoriasis, moderately severe atopic dermatitis and widespread vitiligo, emphasising therapeutic onset and remission duration[12,13].

Keratinocytes, circulating and cutaneous T-cells, neutrophils, monocytes, Langerhans cell, mast-cells and fibroblasts are susceptible to low doses of narrowband UVB and are thus more or less a selective target of the photons.

Ozawa et al. have shown that narrowband UVB causes greater depletion of T cells in psoriatic plaque and induces more rapid apoptosis of dermal T cells than broadband UVB[2]. Low doses of UVB light suppress mast-cell degranulation, histamine release and prevent the UV-induced vasodilatation, being an important therapeutical mechanism in atopic dermatitis and mastocytosis[14]. Immune suppression, alteration of cytokine expression, and cell cycle arrest may all contribute to the suppression of disease activity in psoriatic plaques.

Excimer laser emits monochromatic light at 308 nm wavelength and allows focused delivery of light to limited skin lesions and spares the surrounding uninvolved skin completely. According to several studies, patients with localized psoriatic plaques need fewer treatments with excimer laser in comparison to narrowband UVB phototherapy[15].

The use of this laser is rather limited to treatment of localized plaques due to the small spot size, which makes targeting of large surface areas impractical[16,17].

Westerhof and Nieuweboer-Krobotova reported for the first time that follicular repigmentation in areas affected by vitiligo is improved by twice-weekly narrowband UVB for the maximum period of one year[18]. UV radiation enhances transcription of the tyrosinase gene (via microphthalmia-associated transcription factor), upregulates expression of proopiomelanocortin and its derivative peptides within keratinocytes, melanocytes and other cutaneous cells. In addition, increased activity of Rac1 (involved in dendrite formation), increased kinesin to dynein ratio, and upregulated expression of protease-activated receptor-2 (PAR2; involved in melanosome transfer) stimulate melanocytes dendricity and melanosome transport to keratinocytes. UV radiation results in augmented anterograde transport by increased kinesin and decreased dynein activity[19,20].

The proposed mechanisms of UVB on cutaneous T-cell lymphomas include deterioration of epidermal Langerhans cell function and alterations in cytokine production and adhesion molecule expression by keratinocytes.

Narrowband UVB induces local and systemic immunosuppressive effects which may particularly contribute to beneficial effect of this light source[16].

## Ultraviolet A Therapy and Photochemotherapy

UVA light penetrates deeper into dermal structures, when compared to UVB light. UVA radiation carries less energy than UVB radiation, but due to its long wavelength penetrates the skin the deepest with as much as 50% reaching the dermis. Because of its longer mean wavelength, UVA1 (340–400 nm) radiation penetrates more deeply into the skin than UVA2 (320–340 nm), and thus affects not only epidermal structures, but also mid and deep dermal components, especially blood vessels. UVA effects are dominated by indirect DNA damage caused by reactive oxygen species (ROS) such as singlet oxygen. DNA damage, activation of tumor suppressor genes, growth cytokines withdrawal (e.g. EGF, TGF-α, IGF, PDGF) and activation of cell-death mediators (e.g. TNF) induce apoptosis of the epidermal and dermal cells[21]. DNA damage due to UV radiation upregulates expression of the p53 tumor suppressor gene in the basal and suprabasal layers of epidermis[22]. Affected under p53, individual keratinocytes will stop the cell cycle in G1 phase to allow time for DNA repair (pyrimidine dimer excision) before the cell enters into division phase or apoptosis of keratinocytes (»sunburn cells«) in case of irreparable DNA damage[23].

The regulation of $G_1$, $G_2$ and M transitions involves three major protein families: cyclins, cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CKIs). $G_1$ arrest is mainly caused by p53-mediated activation of CKI which inhibits phosphorylation of retinoblastoma (Rb) protein. Dephosphorylated Rb protein blocks keratinocyte proliferation by binding to and thereby inactivating transcription factor (E2F) required for transcription of $G_1$/S cyclins and cell cycle propagation. Rb dephosphorylation, at the $G_1$ checkpoint blocks cell proliferation and causes $G_1$ arrest[24].

While inhibiting anti-apoptotic (Bcl-2) protein transcription, p53 protein also activates transcription of pro-apoptotic BAX protein. Caspases, apoptosis-related proteases, are then activated by BAX resulting in nuclear DNA fragmentation and degradation of cellular structural proteins such as laminin and actin[21].

Edström et al. noted an increase of Ki67 positive cells in the epidermis and a slight increase of cyclin A positive cells after each cycle of UVA1 irradiation. This positivity indicates that there is an increased proportion of epidermal cells in the $G_1$ phase which results in significant acanthosis[25].

The mechanisms of enhanced keratinocyte apoptosis induced by PUVA (photochemotherapy) and UVA-1 differ. UVA1 irradiation induces both early apoptosis (protein synthesis independent) and late apoptosis of T-lymphocytes, that are relevant in the treatment of atopic dermatitis and mycosis fungoides[26]. It may also reduce the number of Langerhans cells, mast-cells and regulatory

CD4+CD25+ T cells in the dermis in atopic dermatitis, and in cutaneous mastocytosis. Besides inducing apoptosis, photochemotherapy has been implicated in causing other immunomodulatory effects. Researchers have discovered that PUVA decreases mast cell degranulation and histamine release. In addition, it has been shown that UVA1 induces increased expression of matrix metalloproteinase 1, a collagenase which reduces concentration of procollagen and collagen in treated lesions of localized scleroderma, resulting in softening and disappearance of sclerotic skin. Following the completed phototherapy and further regression of the sclerotic area continues[25].

Photochemotherapy utilizes a combination of psoralens and UVA radiation. PUVA is used to treat numerous dermatoses among which psoriasis, atopic dermatitis, vitiligo and cutaneous T-cell lymphoma are well-established indications[27]. Following many years of oral administration of psoralen with UVA, topical regimens such as bath and cream PUVA have been used more frequently. The usage of topical regimens avoids some of the systemic effects of oral psoralen, notably nausea and corneal uptake (protective glasses are required for 24 h after oral PUVA therapy) [28,29]. In the absence of UVA radiation, the psoralen intercalates between DNA base pairs. Absorption of photons in the UVA range results in the formation of unstable complexes 3,4- or 4′, 5′ -cyclobutane monoadduct with pyrimidine bases of native DNA. The 4′, 5′ monoadducts can absorb a second photon and this reaction leads to the formation of an interstrand cross-links in the double helix[4].

Excited psoralens can also react with molecular oxygen. Singlet oxygen, an excited state of molecular oxygen and part of the ROS, is generated during UVA exposure in the presence of photosensitizers. This reaction causes damage to cellular, mitochondrial, and nuclear membranes by epidermal lipid peroxidation leading to massive calcium influx, extensive calcification of the mitochondria, and cell death.

The conjunction of psoralens with epidermal DNA inhibits DNA replication in T-lymphocytes and keratinocytes and causes cell cycle arrest which leads to subsequent inhibition of cell proliferation in several dermatoses. Various mechanisms of action may be involved as well, since PUVA is also effective in nonproliferative diseases. Indeed psoralen photosensitization also alters expression of cytokines and cytokine receptors such as impairment of IL-2 production by T-lymphocytes, inhibition of epidermal growth factor receptor tyrosine kinase activity and inhibition of chemotactic activity of polymorphonuclear neutrophils in response to anaphylatoxin C5a[30].

PUVA decreases expression of Th1/Th17 inflammatory cytokines, specifically IFN-γ, IL-12, and IL-23, within psoriatic lesions and serum[31].

Apart from DNA, psoralens interact with RNA, proteins and other cellular components and indirectly modify proteins and lipids via singlet oxygen-mediated reactions or by generating free radical production.

PUVA can reverse the pathologically altered patterns of keratinocyte differentiation markers and reduce the number of proliferating epidermal cells. PUVA strongly suppresses Infiltrating lymphocytes, which varies depending on different T-cell subsets. PUVA is far more potent in induction of apoptosis in T-lymphocytes and antigen presenting cells than in keratinocytes, which may explain its efficacy in cutaneous lymphomas as well as in inflammatory skin diseases such as psoriasis and atopic dermatitis[32]. According to Marks and Fox, PUVA could lead to apoptosis and modify expression of new oligopeptides in surface MHC molecules, which might be the cause why these cells have a higher level of antigenicity[33].

In addition, PUVA also mediates the downregulation in expression of »homing receptors« (HECA) of epidermotropic malignant T-cell thus PUVA serves as effective treatment modality in early-stage cutaneous T-cell lymphoma[34].

Melanogenesis is also stimulated by PUVA. The process involves the photoconjugation of psoralens to DNA in melanocytes followed by mitosis and subsequent proliferation of melanocytes, which leads to repopulation of the epidermis, increased formation and melanization of melanosomes, enhanced transfer of melanosomes to keratinocytes, and increased synthesis of tyrosinase via stimulation of cAMP activity[18–20].

## Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is a technique which uses UVA irradiation of leukocyte-enriched blood in the presence of psoralen. Photosensitizing agent can be administered orally or directly to the leukocyte/plasma concentrate, which is then subsequently irradiated outside the body in the process of plasmapheresis and returned to the circulation. It is an effective therapeutic regimen for erythrodermic cutaneous T-cell lymphoma. This technique is very potent in induction of apoptosis in T-lymphocytes and modification of lymphocyte cytokine production.

Knobler et al. posed a hypothesis that reinfusion of ECP-treated lymphocytes induces autovaccination against the pathogenic T-cell clones[35].

## Conclusion

Despite the introduction of numerous potent bioengineered systemic medications in the field of dermatology, phototherapy remains established and often preferred option for the most common dermatoses. Still the actual pathways underlying phototherapy in most dermatoses are not known in details, therefore further studies on both clinical and basic photoimmunology will be needed to reach these goals.

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## KORISNOST FOTOTERAPIJE U LIJEČENJU DERMATOLOŠKIH BOLESTI

## SAŽETAK

Fototerapija označava upotrebu ultraljubičastog (UV) svjetla u liječenju nekoliko bolesti kože, a koriste se različite valne duljine ultraljubičastog zračenja. Trenutno, fototerapija obuhvaća širokospektralnu UVB (290–320 nm), uskospektralnu UVB (311–313 nm), 308 nm excimer laser, UVA 1 (340–400 nm), psoralen plus UVA (PUVA) i ekstrakorporalnu fotokemoterapiju – fotoferezu. Međudjelovanje različitih fotobioloških mehanizama za sada nije u potpunosti razjašnjeno. Veliki broj bolesti kože ima dobar terapijski odgovor na fototerapiju, a neke od najvažnijih indikacija su: psorijaza, atopijski dermatitis, T-stanični limfom kože, cirkumskriptna sklerodermija i vitiligo. UVB zračenje prvenstveno djeluje na strukture epidermisa i papilarnog dermisa, dok UVA djeluje na papilarni i retikularni dermis, a osobito na krvne žile. UVB zračenje apsorbiraju endogene kromofore, poput DNA jezgre, čime se potiče cijeli niz biokemijskih reakcija. Apsorpcija UV zračenja od strane DNA dovodi do stvaranja fotospojeva koji dovode do smanjene sinteze DNA. Pored ovog učinka, UV zračenje dovodi do otpuštanja prostaglandina i citokina koji imaju važan učinak u supresiji imunološkog odgovora. UV zračenje smanjuje broj Langerhansovih stanica, T-limfocita i mastocita u dermisu. Također djeluje na molekule u citoplazmi i na staničnoj membrani. Najvažniji mehanizmi fototerapije su apoptoza, lokalna i sistemna imunosupresija, te promjena ekspresije i sekrecije citokina. PUVA je oblik fotokemoterapije kod kojeg se koriste psoraleni i UVA zračenje. Psoraleni stvaraju unakrsne veze s DNA, inhibiraju replikaciju DNA i uzrokoju zaustavljanje staničnog ciklusa. Nakon izlaganja UVA zračenju psoraleni mijenjaju ekspresiju citokina i njihovih receptora. Osim navedenog, psoraleni djeluju na RNA, te ostale strukture stanice i putem slobodnih kisikovih radikala utječu na oštećenje proteina i lipida. PUVA snažno utječe na supresiju limfocita s različitim učinkom na različite podvrste T-limfocita. Psoraleni i UVA zračenje potiču i melanogenezu. Ekstrakorporalna fotofereza je metoda koja se primjenjuje u liječenju eritrodermijskog stadija limfoma kože. Ova metoda snažno potiče apoptozu T-limfocita. Unatoč primjeni različitih učinkovitih sistemnih i bioloških lijekova u dermatologiji, fototerapija ostaje pouzdana terapija izbora u liječenju različitih bolesti kože.